SYNTHETIC THERAPEUTIC AGENTS.

BY

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THE encouraging results which a German medical commission has obtained in the treatment of sleeping sickness in British and Belgian Central Africa by the use of a synthetic drug, the Bayer 205, have recently been discussed. No doubt it is as yet too early to draw final conclusions concerning the efficacy of the new treatment, but certain aspects of the whole large question involved may be profitably reviewed.

Some time ago the *Times* (August 25th, 1922) recorded that at a meeting of the Association of Tropical Diseases held in Hamburg the statement was made that "Bayer 205" is the key to tropical Africa, and consequently to all the colonies, and that the German Government must "be required to safeguard this discovery for Germany; its value is such that any privilege of a share in it granted to other nations must be made conditional upon the restoration to Germany of her colonial empire." Little of the altruism of pure science is discernible in the sentiments expressed at the Hamburg meeting; and, indeed, the fact that the nature of the new remedy is kept a profound secret is sufficient indication that the Bayer Company—one of the chief sections of the great German coal-tar trust—proposes to make a commercial profit and to serve German political ends by treating tropical diseases in the territories of Britain and her allies. The complexities of the issues which will arise if this project is allowed to develop are obvious and do not call for exposition at the moment.

The purpose of the present note is to direct attention to one aspect of therapeutic research which seems to have been neglected in this country, and to show that this neglect, unless remedied, will continue to hamper the treatment of disease and will constitute an ever-rising handicap to British therapeutic science.

During late years it has been increasingly realized that specific pathological organisms are susceptible to attack by particular synthetic chemical substances of generally quite simple chemical constitution. Although certain main types of chemical compound likely to prove of value may in many cases be distinguished, the final choice of the individual substance which should be used has necessarily to be left to the clinician; the selection is, indeed, purely empirical in character. Thus, whilst organic arsenic compounds as a class attack the spirochaete of syphilis in the blood, the most effective curative agent, salvarsan, or Ehrlich's "606," or some closely related substance, was selected by a method of pure trial and error.

For the sake of lucidity we may classify the necessary stages in the search for new synthetic curative agents under three headings. First, the provision by scientifically trained organic chemists of large numbers of related compounds of any particular class which is considered deserving of therapeutic study; secondly, the laboratory study of the effects of these substances on living organisms and physiological fluids; and, thirdly, the clinical study of any compound which the previous laboratory investigation has shown to be worthy of further trial. In Germany these three subdivisions of the problem seem to be very satisfactorily correlated; the investigation of the organo-arsenical drugs, of which the earliest, atoxyl, was a French invention, was taken up by Ehrlich in conjunction with the Höchst Dye Works, vorm. Meister, Lucius, and Brüning, and with the Georg Speyer Hospital in Frankfort; it resulted in the introduction of salvarsan, neosalvarsan, and many other useful aids in the treatment of diseases of protozoal origin.

Apart from the fact that greater facilities exist on the Continent than in England for treating hospital cases as material for research, it is probable that our various great medical research institutions are well able to carry out laboratory and clinical tests on any material submitted to them. There is no doubt, however, that no efficient organization exists in this country for the provision of large numbers of related synthetic products on which laboratory and clinical tests can be made; occasionally an organic chemist submits a chance compound or two for study, but no more than a sporadic interest in the subject has been created. This side of the question has been largely neglected; and yet the preparation of the necessary materials is probably a much more simple matter than is the carrying out of the necessary tests with the materials, whilst, during late years, more work has been done on organic arsenical compounds and organo-metallic compounds by British chemists than by the Germans.

The question under consideration may be illustrated by putting it forward in a rather more concrete form. The synthetic drugs which have proved most serviceable in the modern treatment of protozoal diseases are organic compounds of some element, such as mercury, arsenic, or antimony, which in simpler states of combination is known to be poisonous. Little has, however, been published on the comparative pharmacology of long series of closely related organic compounds of the elements just named; such fundamental knowledge is essential if any logical progress is to be made in establishing a relationship, however roughly, between chemical constitution and physiological action and in selecting further compounds more efficient in their action. A great deal of such correlated knowledge doubtless exists, but it is safely hidden away in the research laboratory records of the German chemical works; it will not be divulged because its publication would undoubtedly increase commercial competition.

The present lack of co-operation between the synthetic organic chemist and the pharmacologist could be met by the establishment of an advisory committee including several of the many competent organic chemists available in this country; it should be the duty of this body to draw up schemes of work on selected subjects involving the preparation of long series of related compounds and the pharmacological and clinical study of such as show promise of useful applications. The preparation of the necessary materials would necessitate the employment of a number of chemists working under the direction of the Committee; the expense thereby incurred would be amply repaid by the results obtained.

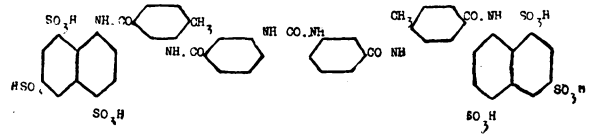
The evils arising from the non-existence of official liaison between the synthetic chemist and such a body as the Medical Research Council are well illustrated by the example of Bayer 205. Although the constitution of this substance is being kept secret, a clue thereto is furnished by recent German patent literature; as Dr. King has pointed out (BRITISH MEDICAL JOURNAL, September 23rd, 1922, p. 569), Bayer 205 is pretty certainly a complex derivative of urea, and a guess can be made as to which particular class of such compounds should be searched for its identification. Doubtless the substance will be found protected by both Continental and British patents; this, however, provides but little safeguard, because the applications of the material are practically confined to tropical colonies as yet too unsophisticated to possess a system of patent law. If the identity of Bayer 205 were revealed the existence of patents covering its preparation would be little obstacle to its manufacture and use.

The work which led up to the discovery of Bayer 205 has been in progress since 1904, the patents on the subject date from 1913, and the substance has been under pharmacological examination for the last four years; yet the nature of the compound still remains a secret. It is safe to assert that a few competent organic chemists, working under the guidance of the committee suggested above, would make Bayer 205, and perhaps an improvement thereon, in less than twelve months.

As the above short note was being dispatched, the *Comptes rendus* of the Académie des Sciences for the meeting of February 11th came to hand, and by a curious coincidence include a paper by Ernest Fourneau and several collaborators on the subject of Bayer 205. These authors state that a review of the patent literature, followed by a systematic investigation which has lasted more than a year, has enabled them to prepare a compound which they believe to be identical with Bayer 205; both show identical physical properties and trypanocidal effects, and it is impossible to discern the least difference between the two products. The

final proof of identity rests, of course, on the chemical comparison of Bayer 205 and the new preparation, Fourneau 309; this is not yet possible as the authors have not the former in their hands.

The constitution of Fourneau 309 is the following:



On comparing this with the constitution suggested by Dr. King (loc. cit.) it will be seen that this chemist was remarkably near the truth in his prognostication.

RICE IN RELATION TO BERI-BERI IN INDIA.*

BY

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PRESENT-DAY views as to the association of true tropical beri-beri with the too exclusive use of a rice diet may be summarized as follows:

1. When decorticated rice is used as the main staple of diet for any length of time beri-beri appears.
2. Outbreaks of the disease disappear when whole or under-milled rice is substituted for decorticated rice.
3. Beri-beri never appears when under-milled rice is eaten.
4. Beri-beri does not occur when parboiled rice is eaten.
5. A rice which contains over 0.4 per cent. of phosphorus pentoxide (P_2O_5) will not cause beri-beri, while one with less than that amount is unsafe if rice forms the principal article of diet.
6. The incidence of beri-beri depends on the treatment to which rice is subjected before consumption.
7. Beri-beri is directly caused by deficiency of a certain vitamin or vitamins in the diet.

I propose in this paper to consider how far these views are applicable to true tropical beri-beri as it occurs endemically in India. In that country, as elsewhere, beri-beri—or, more properly, beri-beri-like maladies—may occur not only in endemic but in sporadic and epidemic form, and may be associated with the use of other foods than rice, but to deal with all three would take more time than I have at my disposal. I shall confine myself, therefore, to the endemic form of the disease, and lay before you the results of my work on this subject during the past few years in India.

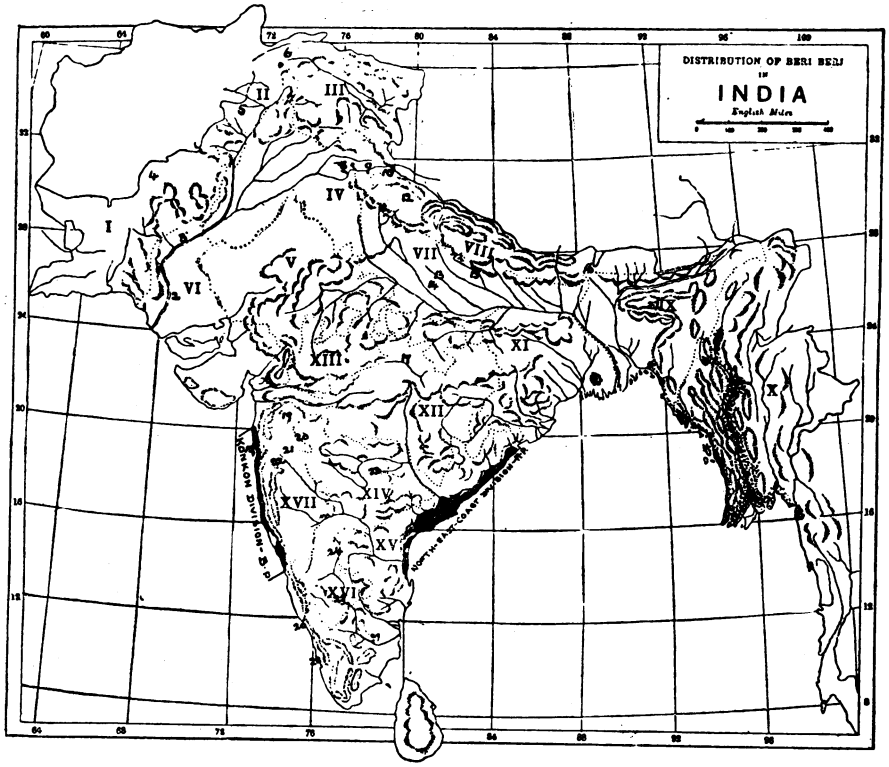

FIG. 1.—I, Baluchistan; II, N.W. Frontier Provinces; III, Kashmir; IV, Punjab; V, Rajputana; VI, Sind; VII, United Provinces of Agra and Oudh; VIII, Nepal; IX, Eastern Bengal and Assam; X, Burma; XI, Bengal; XII, Central Provinces and Berar; XIII, Central India; XIV, Hyderabad; XV, Madras; XVI, Mysore; XVII, Bombay.

The first point to which I would direct attention is that although rice is widely cultivated in India, and is the staple diet of many millions of her peoples, beri-beri is not widely distributed over the peninsula. On the west coast of India, for instance, as much as 60 to 100 per cent. of the cropped area is under rice, while on the east coast as much as 40 to 60 per cent. is under rice. Now the extent to which rice is cultivated in any given locality is a very fair criterion of the extent to which it enters into the dietary of the people of that locality. This being so, and having regard to the profusion of modern rice mills in India at the present time, one would expect beri-beri, in the light of modern views, to be endemic throughout a wide extent of the peninsula. But it is not. The actual distribution of the disease in India and Burma is shown in Fig. 1; it will be noted that the distribution of beri-beri as an endemic is limited to a narrow strip of coastal area situated in the north-east coast division of the Madras Presidency, to a few circumscribed areas in Bengal and Assam, to the coast of Burma, and the valleys of the Irrawaddy and Salween rivers in that Province. Isolated cases, or even small outbreaks, occur from time to time in other parts of India—the sites of these are indicated by Arabic numerals—but these outbreaks are usually confined to troops (British or Indian), to the crews of ships touching at Indian ports, to prisoners in gaols, to certain Chinese communities, and to former residents of endemic areas who have migrated to other parts of India.

In this map I would direct attention to the narrow strip on the west coast which is indicated in black—the Konkan districts of the Bombay Presidency. It is in the same latitude as the similar strip on the east coast of the Madras Presidency, where beri-beri has its endemic home. In the former beri-beri is wholly unknown among the civil population; in it rice cultivation is mainly dependent on rainfall, while in the similar area on the east coast it is dependent on irrigation; in the former the percentage of gross cultivated area under rice is 68, in the latter 38; in the former there are 173 rice mills, producing for the most part *raw, milled, and polished rice*, in the latter 203 rice mills, producing for the most part *parboiled rice* (although they produce also raw, milled, and polished rice for local consumption). The density of the population to the square mile in the strip of coast on the west is 222, in that on the east 345; in proportion to the population there are as many rice mills in the one as in the other. It may safely be inferred that the consumption of raw, milled, and polished rice is as great per head of the population on the west coast as on the east, yet beri-beri is unknown in the former, while it prevails extensively in the other. In both decorticated rice is the main staple of diet of large sections of the community, and with the exception of pulses is the only grain eaten by the rice-eating classes. Clearly, then, if beri-beri be so

* A paper read in the Tropical Section of the Royal Society of Medicine, on March 3rd, 1924.